NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Autologous chondrocyte implantation using chondrosphere for treating symptomatic articular cartilage defects of the knee

1 Recommendations

1.1 Autologous chondrocyte implantation (ACI) using chondrosphere is recommended as an option for treating symptomatic articular cartilage defects of the knee in adults, only if:

- the person has not had previous surgery to repair articular cartilage defects
- there is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis) and
- the defect is over 2 cm^2.

Why the committee made these recommendations

Current surgical treatments for symptomatic articular cartilage defects of the knee include microfracture, ACI and mosaicplasty.

Clinical trial results show that ACI using chondrosphere is as effective in the short term as microfracture, which is the most commonly used surgical option. But it is unclear how well chondrosphere works in the longer term compared with microfracture, because there is little data available beyond 2 years. Chondrosphere has greater benefit in articular cartilage defects larger than 2 cm^2.

Issue date: December 2017

The most plausible cost-effectiveness estimate for chondrosphere compared with microfracture is £4,360 per quality-adjusted life year (QALY) gained. However, this is likely to be an underestimate because it does not accurately consider the long-term effects of microfracture, which are uncertain. Defects larger than 2 cm^2 are often treated by best supportive care. The cost-effectiveness estimate for chondrosphere compared with best supportive care is likely to be lower than £20,000 per QALY gained, for defects larger than 2 cm^2.

2 Information about chondrosphere

Marketing authorisation	Chondrosphere (Spherox, Co.don) is indicated for the 'repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults'.
Dosage in the marketing authorisation	10 to 70 spheroids are applied per square centimetre of defect.
Price	£10,000 per culture per patient, including cell costs and transportation. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 7) considered evidence submitted by Co.don and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

Treatments for articular cartilage defects of the knee include best supportive care and surgery

3.1 The clinical expert explained that the aims of treating symptomatic articular cartilage defects of the knee are to reduce symptoms, restore function and prevent osteoarthritis. The clinical expert confirmed that people with defects will first be offered physiotherapy, corticosteroid injection, pain management and weight loss. If symptoms persist, people will be considered for surgery including knee lavage with or without

debridement, microfracture, autologous chondrocyte implantation [ACI] and mosaicplasty. The choice of surgery depends on the size of the defect, condition of the cartilage and other patient-related factors including previous articular cartilage knee repair surgery, age and body mass index (BMI). The committee understood that in current clinical practice, the preferred surgery for defects larger than 2 cm^2 would be ACI, provided that the person has minimal osteoarthritis (if any) and no history of previous cartilage repair surgery for the affected knee (see NICE's technology appraisal guidance on ACI for treating symptomatic articular cartilage defects of the knee [TA477]), but that ACI is not widely available (see section 3.3). If symptoms persist after microfracture or ACI, people could have mosaicplasty or further ACI. When all other options have been exhausted, osteotomy, partial and total knee replacement are considered later in the treatment pathway.

Autologous chondrocyte implantation using chondrosphere

Chondrosphere would provide a surgical option for articular cartilage defects larger than 2 cm^2

3.2 The committee noted that no submissions or expert nominations were received from any patient or professional organisations invited to participate in this appraisal. The clinical expert highlighted that microfracture is commonly used, including for salvage procedures, because it is inexpensive and minimally invasive. However, the expert noted a growing trend of limiting microfracture to smaller defects, with thresholds ranging from 2 to 4 cm^2. Although TA477 recommends ACI for defects larger than 2 cm^2, the committee noted that there is currently no good surgical alternative to microfracture (see section 3.3). It concluded that there are limited options available for managing articular cartilage defects, particularly those larger than 2 cm^2.

Comparators

The most relevant comparators are microfracture (for defects up to 2 cm^2) and best supportive care (for defects larger than 2 cm^2)

3.3 The final scope issued by NICE listed a number of comparators, depending on defect size. The committee appreciated that there is variation in the use of these procedures in clinical practice, because of the experience and preference of the treating clinician and the availability of treatment. However, it concluded that the most relevant comparators for this appraisal are microfracture and best supportive care:

- Microfracture – the committee heard from the clinical expert that this option is used only for small defects, usually up to 2 cm^2. It agreed that microfracture is a relevant comparator for defects up to 2 cm^2, in line with current clinical best practice (see section 3.1).
- ACI – the ERG highlighted that ACI is not widely available in the NHS. 'Traditional' ACI is currently available at 1 centre in England, under hospital exemption on a non-routine basis. The committee was aware that 2 other ACI technologies were appraised in TA477 (ChondroCelect and MACI) but both of these no longer have marketing authorisation in the UK. The committee agreed that 'traditional' ACI cannot be considered standard care because of its limited availability in the NHS, and therefore concluded that it is not a relevant comparator.
- Knee debridement – the company noted that this option is used before or after ACI or microfracture. The committee agreed that knee debridement is not a relevant comparator.
- Mosaicplasty – the ERG noted that mosaicplasty is rarely used in NHS clinical practice. The committee agreed that this option is rarely used in NHS clinical practice and therefore is not a relevant comparator.
- Best supportive care (non-surgical options) – the committee agreed that there are limited surgical options available for defects larger than 2 cm^2 (see section **Error! Reference source not found.**). Therefore, it

concluded that the most relevant comparator for defects larger than 2 cm^2 is best supportive care.

Clinical evidence

The clinical evidence for chondrosphere came from 2 trials

3.4 Two trials on chondrosphere used the primary outcome of a 10-point improvement in overall Knee injury and Osteoarthritis Outcome Score (KOOS) from the day of the surgical procedure:

- A dose-finding study: a phase 2, randomised, open-label, multi-centre, parallel arm trial in 75 adults (18 to 50 years) with a single ICRS Grade III or IV knee defect (37% femur, 63% patella) ranging in size from 4 to 10 cm^2. It compared low, medium and high doses of chondrosphere (3 to 7 spheroids/cm^2, 10 to 30 spheroids/cm^2 and 40 to 70 spheroids/cm^2).
- COWISI: a phase 3, randomised, open-label, multi-centre, parallel arm, non-inferiority (non-inferiority margin of 8.5% in overall KOOS) trial of 102 adults (18 to 50 years) with a single ICRS Grade III or IV knee defect (99% femur, 1% patella) ranging in size from 1 to 4 cm^2. It compared chondrosphere (mean dose 25±16, range 7 to 70 spheroids/cm^2) with microfracture.

The committee noted that the trials were different at baseline in defect size and location. The clinical expert explained that the average defect size on a German registry is 3.7 cm^2, with a large proportion of defects ranging in size from 4 to 5.5 cm^2. The committee considered it likely that the population having treatment in Germany is broadly similar to patients seen in the NHS in England. The expert explained that femoral defects are the most common, followed by patella defects, and recent evidence suggests that patella defects do not have worse outcomes after ACI than femoral defects. The committee considered the baseline proportion of people with traumatic knee defects (42% in COWISI) and proportion of smokers (33% in COWISI). The clinical expert stated that the imbalance

between the 2 trials in traumatic knee defects and smokers does not represent an important clinical difference. The committee agreed that the trial populations are generalisable to patients likely to be seen in the NHS.

Indirect clinical evidence from a network meta-analysis is not relevant because the ACI comparators are not licensed in the UK

3.5 Indirect clinical evidence came from a network meta-analysis on the response and failure rates from 3 ACI trials (chondrosphere and 2 other ACI technologies, ChondroCelect and MACI) with microfracture as a common comparator. The ERG was concerned that the 3 trials were severely imbalanced at baseline in several factors that are likely to affect treatment outcomes: defect size, previous articular cartilage knee repair surgery and level of disease burden assessed by KOOS. The committee agreed that it is not appropriate to combine the trials in a network meta-analysis because of these differences. It noted that the ACI comparators (ChondroCelect and MACI) are not relevant to this appraisal because they do not have current marketing authorisation in the UK (see section 3.3). The committee recalled that 'traditional' ACI is available at 1 centre in England, under hospital exemption on a non-routine basis (see section 3.3), but had not been included because there is currently no published data available that enables a network meta-analysis to be done. Therefore, the committee concluded that the most relevant clinical evidence is from COWISI, which provides direct evidence of chondrosphere compared with microfracture.

Chondrosphere is at least as effective as microfracture at 2 years for defects of 1 to 4cm^2, with a greater difference observed in defects over 2cm^2 up to 4cm^2

3.6 The clinical expert confirmed that the minimal clinically important difference in overall KOOS of 8.5 points in COWISI is consistent with clinical practice. The committee noted that chondrosphere is non-inferior to microfracture for all defect sizes (1 to 4 cm^2). However, it noted that the

improvement from baseline in overall KOOS at 2-year follow-up was numerically greater in patients who had chondrosphere compared with microfracture. The committee also noted that the difference in overall KOOS between chondrosphere and microfracture was greater for larger defect sizes (2 to 4cm^2) compared with smaller defect sizes (1 to less than 2cm^2). It noted that the proportions of responders (defined as those achieving a 10-point improvement in overall KOOS) were similar for chondrosphere and microfracture at 2 years. The committee concluded that chondrosphere is at least as effective as microfracture.

Chondrosphere improves outcomes at 4 years for larger defects ranging in size from 4 to 10 cm^2

3.7 The committee noted that there is little long-term data available on chondrosphere compared with microfracture. It agreed that the phase 2 study (see section 3.4) provides non-comparative evidence of the longer-term effect of chondrosphere at 4 years and in larger defects. It noted that there was continual improvement in overall KOOS from baseline at 1 year and up to 4 years, and the differences were clinically significant. The ERG stated that the benefit of ACI is likely to be seen over the longer term based on observational studies included in TA477. The committee agreed that the long-term benefit of chondrosphere is uncertain. However, it concluded that chondrosphere improves outcomes at 4 years and for larger defects.

Company's economic model

Model structure

3.8 The company used a Markov model to assess the cost effectiveness of chondrosphere compared with microfracture and other ACI technologies. It modelled 2 possible treatments in sequence. The model used a lifetime horizon of 100 years, a cycle length of 1 year and transitions between each health state at the end of each cycle. The model population included

60% men and had a starting average age of 33 years. The model was divided into 2 parts, up to and after 55 years:

- Up to 55 years patients could have knee repair surgery and be in the following health states: primary repair, successful primary repair, second repair, successful second repair and no further repair. The model allowed 2 outcomes after primary or second repair; permanent success (staying in the successful primary or second repair health states) or temporary success (repair fails after being symptom free for years; patients can decide to have a second repair or no further repair). Patients could also move into the 'death' state at any time.
- After 55 years patients could have knee replacement and be in the following health states: first knee replacement, successful first knee replacement, further knee replacement, successful further knee replacement and no further knee replacement. The model allowed 2 outcomes after first or further knee replacement; permanent success (no further replacement or staying in the successful further knee replacement health state) or temporary success (further knee replacement or no further knee replacement). Patients could also move into the 'death' state at any time.

The committee noted that the company's model was broadly similar to the model in TA477. The main difference is that the model did not allow movement from successful primary repair to no further repair, only to a second repair. The ERG explained that the company's model would therefore likely overstate the treatment benefits for ACI (including chondrosphere) because patients in the 'successful primary repair' health state have a higher utility value than those in the 'no further repair' health state. However, the committee noted that the probability of a second repair in the model is very small and has little effect on the cost-effectiveness estimates. The committee concluded that although it would prefer a model that allows movement from successful primary repair to no further repair, the company's approach is acceptable.

The most relevant treatment sequences are microfracture only, chondrosphere only and chondrosphere followed by chondrosphere

3.9 The company modelled the same treatment sequences included in TA477:

- microfracture followed by microfracture
- microfracture followed by ACI
- ACI followed by microfracture
- ACI followed by ACI.

In the company's model, ACI could be chondrosphere, ChondroCelect or MACI and the primary and second ACI are assumed to be the same. The committee noted that the probability of second repairs is very low in the company's model and heard from the clinical expert that ACI followed by microfracture is an unlikely treatment sequence in clinical practice. The committee was aware that TA477 recommends ACI only for people with no previous articular cartilage knee repair surgery. The clinical expert suggested that microfracture followed by ACI is sometimes used in clinical practice. However, the committee noted that ACI is not recommended in people with previous articular cartilage knee repair surgery, including microfracture. Therefore, the committee agreed that microfracture followed by ACI is not a relevant treatment sequence. The committee considered that the only relevant comparator is microfracture (see section 3.3) and concluded that the only relevant treatment sequences are:

- microfracture only
- ACI followed by microfracture
- ACI followed by ACI.

Assumptions in the economic model

Assuming that the utility value of a successful microfracture returns to baseline level after 5 years is arbitrary and may favour ACI

3.10 The committee noted that, like the model in TA477, the company's model assumed that after successful microfracture the utility value returns to the baseline value after 5 years (that is, from 0.82 to 0.65). In TA477, the committee considered that this was equivalent to assuming that microfracture had failed in all people at year 5. In this appraisal, the clinical expert explained that decline in knee function would likely start at 1.5 years after microfracture. The committee agreed that reducing the utility value for microfracture after 5 years was arbitrary and may have biased the results in favour of ACI. It noted that the company had done a sensitivity analysis in which the utility value of a successful microfracture at 5 years and beyond was maintained at 0.82. The committee understood that removing the assumption that utility decreased over time following a successful microfracture would likely increase the company's base-case incremental cost-effectiveness ratio (ICER). The committee would have preferred the model to adjust for the rate of loss of benefit following microfracture more explicitly, by changing the transition probabilities instead of the utility value of the successful repair health state. In the absence of such analysis, the committee accepted the assumption that there is no further benefit of microfracture after 5 years, but agreed it underestimated the ICER.

Clinical effectiveness inputs and transition probabilities

Concerns about the modelled clinical effectiveness and transition probabilities mainly relate to other ACI technologies

3.11 The committee noted the concerns from the ERG about how the company had derived its clinical effectiveness inputs from the network meta-analysis results, which subsequently informed the transition probabilities in the model. The committee noted that these concerns largely affect the other ACI technologies, ChondroCelect and MACI. It noted that a network meta-analysis is not appropriate and that the data from COWISI, which provide direct evidence of chondrosphere compared with microfracture, are preferred (see section 3.5). The committee noted the ERG's scenario

analyses using direct evidence from COWISI, and it concluded that these analyses are most appropriate for decision making.

Costs in the economic model

The committee preferred the ERG's cost inputs

3.12 The ERG explained that it had applied the committee's preferred procedure costs from TA477 in this appraisal:

- £870 (Health Resource Group code HB25F) for cell harvesting, compared with £734 in the company's model, and
- £2,396 (Health Resource Group code HB25F) for cell implantation, compared with £1,065 in the company's model.

The ERG also explained that it had corrected the company's outpatient visit costs from £121 (paediatric trauma/orthopaedics) to £110 (trauma/orthopaedics). The committee accepted the ERG's changes to these costs.

Cost-effectiveness estimate

The committee preferred the ERG's scenario analyses using only COWISI data

3.13 The committee concluded that the most relevant comparators for this appraisal are microfracture for defects up to 2 cm^2 and best supportive care for defects larger than 2 cm^2 (see section 3.3). Therefore, it preferred the following assumptions:

- direct evidence from COWISI data rather than the network meta-analysis (see section 3.4 and section 3.11)
- treatment sequences of microfracture only, chondrosphere only and chondrosphere followed by chondrosphere (see section 3.9)
- no further benefit of microfracture after 5 years (see section 3.10), although it noted that this is likely to underestimate the ICER
- the ERG's cost inputs (see section 3.12).

The ERG included all of these assumptions and inputs in its scenario analyses. The committee concluded that the ERG's scenario analyses are most relevant for decision making.

Chondrosphere is likely to be a cost-effective option for treating articular cartilage defects of the knee larger than 2 cm^2

3.14 When microfracture is assumed to return to baseline utility values after 5 years, the ICERs are £4,360 per quality-adjusted life year (QALY) gained for chondrosphere only compared with microfracture only, and £5,294 per QALY gained for chondrosphere followed by chondrosphere compared with microfracture only. The committee noted that there is considerable uncertainty surrounding the ICERs because the long-term benefit of chondrosphere is yet to be established (see section 3.7). It also noted that the low ICERs are largely due to the decline in the utility value for microfracture after 5 years, which underestimates the ICERs (see section 3.4 and section 3.10). The committee was aware that most patients with larger defects are likely to have best supportive care in clinical practice (see section 3.3), and the clinical benefit of chondrosphere compared with best supportive care is likely to be greater than when compared with microfracture. The committee had decided that other forms of ACI are not relevant comparators in this appraisal, because they are not widely available in the NHS (see section 3.3). However, it noted that chondrosphere is cheaper than many of the other ACI technologies appraised in TA477 (£10,000 for chondrosphere cell costs, compared with £9,300 to £18,300 for the technologies in TA477). The committee recalled that the population in COWISI did not have previous knee surgery to repair articular cartilage defects, and agreed that it would be appropriate to only recommend chondrosphere in the same population. Because of the uncertainties related to the comparison with microfracture, the committee agreed that it would be appropriate to recommend chondrosphere only for defects larger than 2 cm^2. Therefore, the committee applied similar conditions as in TA477 and concluded that

chondrosphere is a cost-effective use of NHS resources for defects larger than 2 cm^2, in people with no previous surgery to repair articular cartilage defects and minimal osteoarthritic damage to the knee. The committee noted that the recommendation in TA477 specifies that ACI is only done in a tertiary referral centre. This is because the laboratory that makes the only licensed ACI technology available at the time of TA477 is affiliated with a tertiary referral NHS orthopaedic hospital. However, the committee agreed that this caveat is not relevant for this appraisal because there is no such constraint on the use of chondrosphere and that removing it would avoid restricting access to treatment. The company stated that although it had not specifically made a case for chondrosphere in the population for which ACI is recommended in TA477, it would be satisfied with a similar recommendation.

Other factors

There is an unmet need for the treatment of articular cartilage defects in the NHS

3.15 The committee agreed that there is an unmet need because currently ACI is not widely available in the NHS, and there are no good alternative surgical options for people with defects larger than 2 cm^2.

Chondrosphere is innovative but the health benefits are already captured within the economic modelling

3.16 The company explained that it considers chondrosphere to be innovative. The committee noted that chondrosphere is an improved ACI technology that does not need fibrin glue or a cover flap, and does not include any animal derivatives. The committee considered chondrosphere to be innovative but did not identify any additional health benefits not already included in the economic modelling.

The recommendation does not exclude access to chondrosphere for people who are eligible to have it

3.17 The committee considered its recommendation in the context of the equality legislation. It was aware that 1 of its criteria for treatment (that is, minimal osteoarthritic damage to the knee) excludes people with advanced or severe osteoarthritis, which can be disabling. However, one of the contraindications in the marketing authorisation for the technology is advanced osteoarthritis. The committee did not stipulate any specific threshold for the level of osteoarthritis, but instead states in the recommendations that it is appropriate for clinicians experienced in investigating knee cartilage damage to assess suitability for chondrosphere using a validated measure for osteoarthritis of the knee. The committee was therefore satisfied that it has mitigated, as far as it can, any potential unfairness.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has symptomatic articular cartilage defects of the knee larger than 2 cm^2 and the doctor responsible for their care thinks that

chondrosphere is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Recommendations for data collection

5.1 The committee noted that there is little long-term data available on chondrosphere and agreed that data should be entered into a register, including defect size and location in relation to outcomes.

6 Review of guidance

6.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Sanjeev Patel
Vice Chair, appraisal committee
December 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sharlene Ting
Technical Lead

Jasdeep Hayre
Technical Adviser

Jeremy Powell
Project Manager

ISBN: [to be added at publication]